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OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT
APPEALS AND INTERFERENCES

PAPER NO.: 36

Examiner: Low
Art Unit: 1804



Application Serial Number: 08/147,912
Filing Date: 3 November 1993
Appellant(s): Wahl *et al.*

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Stephen E. Reiter
For Appellant

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## EXAMINER'S ANSWER

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This is in response to appellant's brief
on appeal filed on 2 October 1995

The statement regarding the real party of interest and the related appeals and interferences at pages 1-2 of the 2 October 1995 Appeal Brief is noted.

(1) Status of the claims.

The status of the claims contained in the brief is correct

(2) Status of the Amendments after final.

The appellant's statement of the status of amendments after the final rejection contained in the brief is correct.

(3) Summary of the invention.

The summary of the invention (pages 4 and 5) in the brief is noted but contains errors. Specifically, the first FLP recombination target site does not integrate at a specific site - it is random and the instant application does not demonstrate nor teach how to obtain integration of the first such site a specific locus in the genome. For example, there is no disclosure of how one would have effected the integration of that site at a point in the genome that is an unsequenced intron (i.e., non coding domain of a gene) such as for cholesterol ester synthase which is a gene that has not yet been cloned or sequenced nor has the DNA for same been isolated. Insofar as the integration of the first FLP recombination target site is random, there is no apparent disclosure that the recombination with the second DNA that recombines with the first FLP recombination target site recombines solely with and only at that first FLP recombination target site as the second DNA is indicated in the present application to contain an additional gene (see page 13 of the present specification) which can also recombine. Thus, it is apparent that the issue of "randomness" is not solved nor is it apparent that when there are a multiplicity of FLP recombination target sites randomly integrated into the genome of a cell (as the present application does not demonstrate that one and only one DNA with a sequence for an FLP recombination site is integrated) that only one but not all can be modified at a time - e.g., when there are for example, three (3) sites (A, A', and A'), there is no indication that for example that the second DNA can be targeted solely to A without targeting A' and A" nor is there any indication that the second DNA would not also have recombined at another site B that is none of A or A' or A" wherein A, A' and A" are functionally, structurally, and informationally equivalent as DNA is an informational

molecule. Thus, summary in appellant's brief is deficient and a succinct summary of the invention follows.

Summary of the Invention

The present invention is a method for randomly integrating one or more FLP recombination sites into the genome of a cell because the instant brief at page 6 indicates "Integration of the initial FLP recombination site is not targeted" for recombination at such sites with a second DNA at one or more of the FLP recombination sites sites and the second DNA may or may not also recombine randomly at other sites in the genome of the cell. Thus, where the first site is not specifically targeted (Applied here are the accepted dictionary definitions for the words. The "precisely targeted integration" is read exactly for what it is - "precisely" as meaning exactly and "targeted" as a mark to shoot at or for and "integration" as meaning incorporation where the instant brief at in the first sentence of the paragraph bridging pages 6-7 admits that the process is not precise since the initial site is not targeted (i.e, it is not a mark to shoot or aim for, i.e., it is random) the second DNA that combines with the FLP recombination site is not specific since the first such site is admitted as not specifically targeted.

(4) Issues.

The brief contains a statement of the issues, however, the sole issue is that given the stated grounds of objection and rejection, the claims are not patentable because the written description does not demonstrate specificity of integration of the FLP recombination site (the instant brief at page 6 indicates "Integration of the initial FLP recombination site is not targeted") nor demonstrate specificity of one site over another nor demonstrate that recombination does not occur at sites other than the FLP recombination site where the claims are indefinite. Moreover, the claims are anticipated and are obvious over the cited prior art as Golic *et al.* and Sauer *et al.* provide anticipation and obviousness as Golic *et al.* disclose site specific recombination using DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation a process of that recombination where Sauer teaches site specific recombination of mammalian cells via plasmids with the DNA coding for *crellox* where it would have been obvious to use DNA coding for FLP and FRT in vectors for transforming cells as Golic *et al.* disclose site specific recombination with DNA coding for FLP and FRT

where FRT bearing plasmids are directed to the site of an FRT already resident in the genome and thereby indicating use in germline transformation resulted in a transgenic animal where it is indicated that the authors "... expect that it will work in other organisms as well" motivate one of ordinary skill in the art to combine the teachings of Sauer for site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic *et al.* teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the recited steps in the claims into the subject where the subject is another yeast cell and where Golic *et al.* disclose mating the flies, it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other gamete which after fertilization becomes a transgenic fruit fly. Where the Palmiter *et al.* reference which discloses introduction of the transforming DNA into totipotent teratocarcinoma cells or embryonic stem cells which can be introduced into the developing embryo by aggregation of the cells, Sauer taken with Golic *et al.* as discussed above disclose the plasmids with the FLP and FRT DNA for site specific recombination which made it is obvious to modify the process by using totipotent teratocarcinoma cells or embryonic stem cells, i.e., mammalian cells.

(5) Grouping of Claims.

The appellant's statement in the brief indicates that claims 25 and 28 should be considered separately on the basis of the rejections of claims. It is not persuasive because 37 C.F.R. 1.192(c)(5) indicates that for each ground of rejection the claims stand or fall together but where appellant states that claims 25, 26, and 28 should be considered separately, the present brief on appeal does not provide in 37 C.F.R. 1.192(c)(6) under the section "ARGUMENT", any reasons or discussion of separate patentability of these claims over any other claims. Thus, the brief does not comply with the criterion set forth in 37 C.F.R. 1.192(c)(5). Since appellant does not present any argument as to separate patentability of claims 25, 26, and 28, they should not be considered separately because there are no reasons to do so.

(6) Claims Appealed.

A substantially correct copy of the appealed claims appears in the appendix of claims (APPENDIX A). In APPENDIX A, claim 46, the comma "," after "Claim 45" is missing.

(7) Prior Art of Record.

The following is a listing of the prior art relied upon in the rejection of the claims under appeal.

Golic *et al.* 1989 Cell 59: 499-509.
US, Patent 4,959,317 (Sauer), issued 25 September 1990, filed 29 April 1987.
Palmiter *et al.* 1986, Ann. Rev. Genet. 20: 465-499.

(8) New Prior Art.

No new prior art has been applied in this examiner's answer.

(9) Grounds of rejection.

The following ground(s) of rejection are applicable to the appealed claims.

The specification remains objected to under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description and enablement for practicing the claimed invention because the specification does not disclose how the initial FRT site is precisely inserted (i.e., targeted) to the specific DNA (the instant brief at page 6 indicates "Integration of the initial FLP recombination site is not targeted"). Note that the present claim indicates that the precisely targeting applies to both the DNA of item (I) and (ii) of, for example, claim 25 but where the instant brief at page 6 indicates "Integration of the initial FLP recombination site is not targeted" for recombination at such sites with a second DNA at one or more of the FLP recombination sites and the second DNA may or may not also recombine randomly at other sites (preexisiting but unknown and/or additional randomly inserted sites) in the genome of the cell. Precise genomic targeting requires not only precise targeting of the initial insert DNA but that the location to which it is to be inserted also be precisely identified. Absent such teaching, it cannot be said that the DNA to be targeted to the first preexisting site is precisely targeted to some known location on a DNA when that location on the DNA is unspecified. Since the integrating DNA recombines with the FRT site, but where the location of the preexisting site is unspecified, there is

no precise targeting of the integrating DNA to any specified location in the genome; i.e., the problem of inability to control the initial slocation of integration of the initial FRT site remains as the specification does not disclose how the initial FRT is integrated at predetermined sites on a chromosome. See present specification page 12, paragraph bridging pages 12-13. How is the first FLP site specifically and precisely integrated into the genome as for example, one and only one site defined by a specific sequence of bases on a specified chromosome? Note that the first full paragraph of present specification page 12 does not detail how this is done and is subject to the inability to control the site of integration referred to at present specification page 1 and as admitted in the brief in the first sentence of the paragraph bridging pages 6-7 "Integration of the initial FLP recombination site is not targeted".

Claims 25, 26, 28, 42-46, and 48 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 25, 26, 28, 42-46, and 48 stand rejected under 35 U.S.C. 112, first paragraph, as the disclosure is not enabled for precisely targeting the DNA to a predetermined site of that integration, i.e., the first FLP recombination target site is not precisely predetermined by its own location in the genome of the cell. From the present specification, there is no disclosure of how this is accomplished. How does the first FLP site become specifically and precisely integrated into the genome? Note that the first full paragraph of present specification page 12 does not detail how this is done and is subject to the inability to control the site of integration referred to at present specification page 1 and as indicated in the present brief at page 6 (see the "Integration of the initial FLP recombination site is not targeted". Here, where the specification does not disclose how this is done, it would have required undue experimentation on the part of one skilled in the art to have used the present application disclosure to precisely place the first FLP target recombination site at a prespecified location defined at least by chromosome number and specific sequence of bases where there are no other inadvertent sites where the first FLP recombination target site becomes integrated into the genome. Note that the present claims call for the first FLP target recombination site to be precisely placed else the precise location of the integrating DNA is not definable. See MPEP 706.03(n) and 706.03(z).

Claims 25, 26, 28, 42-46, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite as lines 1-2 recitate precisely targeting a DNA but do not indicate that it is only the second DNA and it is only preferentially targeted. As presently recited, the claim also calls for precise targeting of the first DNA as the "a nucleic acid" refers to both the first and second DNA fragments. Claim 26 is indefinite as it calls for excision of the DNA however, the presence of the same enzyme in claim 25 effects an insertion recombination. Note that it is expected that the same steps effect the same result. What is the result of treating the host cell DNA with the enzyme? Is it recombination by insertion or excision? The same step (putting the DNA into the presence of the enzyme to effect catalytic recombination cannot by thermodynamics and entropy run forwards and backwards under the same conditions but for dynamic equilibrium (i.e., substrates of two DNAs are formed into one product (insertion) as fast as the reverse reaction is carried out (i.e., substrate of one DNA is excised to form product (two DNAs). Note that for claims 25 and 26, the conditions (i.e., time, temperature, concentration, pH, etc. under which the enzyme is used are not *per se* indicated as demonstrably different in the claims. In claim 28, the presence of the third FRT is noted, but said claim is also indefinite as to whether or not the first and third sites, first and second sites, as well as the second and third sites recombine in the presence of the recombinase. The claims indicate no specificity for interaction with only one selected site and, thus, where the first and second sites have recombined, there is no indicated specificity to for only recombination with sites 1 and 3 but not 2 and 3. Thus, claim 28 is indefinite. Claim 42 as well as claim 44 are indefinite as to the site specificity (see the reasons above as to claim 25 with regard to the "precisely targeting"). In claims 43 and 44, where the first site is not targeted (as admitted in prior responses and page 6 of the present brief) the claim is not clear as to how one and only one in a multiplicity of sites is precisely targeted to a gene of interest. In claims 42 and 43, it is also not clear as to the metes and bounds of a partial coding sequence as to whether it refers to the DNA of the '5-end, the 3'-end, the middle or both ends, or whether it refers to DNA wherein every other codon has been removed or contains substitutions. Claim 43 is indefinite as to "FRT(s)" and "is/are" as it is not clear whether the claim recitation of "FRT(s)" refers to a single or a multiplicity of "FRT" sites. Claim 48 is indefinite as when the first DNA is integrated into the genome, it

is no longer present as a first DNA, and thus, it is not clear how a second DNA recombines with a first DNA that no longer exists as a first DNA. Claims 42 and 48 are also indefinite as the reference to "a first gene of interest" infers a "second gene of interest" but which is not indicated in claim 42 or 48. In the pending claims it is also unclear as to whether or not the cells contain any naturally occurring FRT sites, the unknown location of which would affect the recited "precise targeting". What defines "a partial coding sequence" (claim 44)? What functional portions are referred to in the claims and how big is a partial coding sequence in nucleotide bases (is it one base or $5X10^6$ bases)?

Claims 25 and 28 stand rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Golic *et al.* which discloses site specific recombination in *D. melanogaster* using DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation which would have resulted in a process for producing the host organism. The step of mating the flies (page 500), is a step of introducing into the cells (which are indicated as already having an FRT site (page 499) in the *w* gene) that are the male or female gametes into the other *D. melanogaster* gamete wherein Golic *et al.* disclose that FLP catalyzed recombination between FRTs in the germline and the soma. In the alternative, it would have been obvious from the disclosure which indicates that "we expect that it will work in other organisms as well" to expect the process to function in other organisms which are higher eukaryotes (page 499, left column) where mammalian cells (page 499 right column) are known higher eukaryotic cells. Where from the Golic *et al.* reference, it would have been anticipated (anticipation being the epitome of obviousness) if not obvious to have expected that the FRT/FLP yeast system which is more closely related to mammalian systems to work in a mammalian system as is evident from the reference.

Claims 25, 26, 28, 42-46, and 48 stand rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.*

Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the *cre* and *lox* (cols 1, 6-7). Where Sauer does not explicitly disclose the use of DNA coding for FLP and FRT, it would have been obvious to one of ordinary skill in the art to use DNA

coding for FLP and FRT in vectors for transforming *D. melanogaster* because Golic *et al.* discloses site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect that it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic *et al.* teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic *et al.* disclose mating the flies (page 500), it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other *D. melanogaster* gamete which after fertilization becomes a transgenic fruit fly. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was a whole, clearly prima facie obvious.

Claims 25, 26 and 28 stand rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.* as applied to claims 25, 26, 28, 42-46, and 48 above, and further in view of Palmiter *et al.* as directed to the "mammalian host cell" as being in a transgenic animal for the reasons indicated in the Office Actions of this and the parent application as restated below.

Sauer and Golic *et al.* are applied as indicated above and where Golic *et al.* indicates expectation of success as indicated above, one of ordinary skill in the art would have found it obvious to combine the teachings in the Palmiter *et al.* reference which discloses introduction of the transforming DNA into totipotent teratocarcinoma cells or embryonic stem cells which can be introduced into the developing embryo by aggregation of the cells. Here, where Sauer taken with Golic *et al.* disclose the plasmids with the FLP and FRT DNA for site specific recombination, it would have been obvious to one of ordinary skill in the art given that Golic *et al.* indicate that "we expect that it will

work in other organisms as well", to modify the process by using totipotent teratocarcinoma cells or embryonic stem cells as disclosed by Palmiter *et al.* which are later aggregated with the developing mouse embryo. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

(10) New Ground(s) of rejection.

This examiner's answer does not contain any new ground of rejection.

(11) Response to Argument.

The commentary in the Appeal brief has been noted and considered but is not persuasive.

The objection to the specification and the rejection of claims 25, 26, 28, 42-46, and 48 under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description and enablement for practicing the claimed invention.

The discussion (pages 6 first paragraph under item 1) is noted as referring to a two step process. This is not persuasive nor addresses the reasons indicated in the stated objection. In the paragraph bridging pages 6-7, appellant states the reason for the objection because "Integration of the initial FLP recombination target site is not targeted". In other words it is not precise. It is random. The claim requires the integration events be precise. Insofar as this paragraph refers to various methods to identify integrable DNA fragments, the precise site of integration of such fragments is random and undefined. Here, it is the first integration site that is unspecifiable and that is what results in the inadequate written description and lack of enablement for the invention as is presently claimed because the requirement of precise is applied to all integrating events using the DNA encoding the FLP recombination site and includes the first integration of such a DNA into the genome of the cell. It is noted that appellant argues that the subsequent integration events are precise, however, where the location of the initial FLP recombination target site is not specified nor predetermined by a specific sequence of bases on a specific chromosome, there is no precision to the process because even where the DNA of claim 25, item (ii) is preferential to the FLP recombination site, the location of that first (initial) site is unspecified and at a random point or points in the genome (for multiply integrated

sites). Thus the comments in the paragraph spanning pages 6-7 and first full paragraph of page 7 are not persuasive.

In the last full paragraph of page 7, it is noted that appellant assertst that appellant can act as their own lexicographer, however, what is applied here are the accepted dictionary definitions for the words. The "precisely targeted integration" is read exactly for what it is - "precisely" as meaning exactly and "targeted" as a mark to shoot at or for and "integration" as meaning incorporation where the instant brief at in the first sentence of the paragraph bridging pages 6-7 admits that the process is not precise since the initial site is not targeted (i.e, it is not a mark to shoot or aim for, i.e., it is random). Thus, the comments in the brief are not persuasive.

> Claims 25, 26, 28, 42-46, and 48 stand rejected under 35 U.S.C. 112, first paragraph, as the disclosure is not enabled for precisely targeting the DNA to a predetermined site of that integration, i.e., the first FLP recombination target site is not precisely predetermined by its own location in the genome of the cell.

Item 2 of brief page 8 asserts that the invention is enabled, however, it is apparent from the disclosure that for precisely targeting the DNA to a predetermined site of that integration, i.e., the first FLP recombination target site must also be precisely targeted and has not been demonstrated in the present application. The "precisely targeted integration" is read exactly for what it is - "precisely" as meaning exactly and "targeted" as a mark to shoot at or for and "integration" as meaning incorporation where the instant brief at in the first sentence of the paragraph bridging pages 6-7 admits that the process is not precise since the initial site is not targeted (i.e, it is not a mark to shoot or aim for, i.e., it is random). The inserted DNA location of the initially inserted DNA encoding the FLP recombination site is not *a priori* precisely predetermined prior to it is integration into the genome of the cell (note the admission at page 6 of the present brief). From the present specification, there is no disclosure of how this is accomplished. How does the first FLP site become specifically and precisely integrated into the genome at predetermined sequence on a predetermined chromosome? Note that the first full paragraph of present specification page 12 does not detail how this is done and is subject the inability to control the site of integration referred to at present specification page 1. Here, where the specification does not disclose how this is done, it would have required undue experimentation on the part of one skilled in the art to have used the present application disclosure to precisely place the first

FLP target recombination site at a prespecified location and where there are no other inadvertent sites where the first FLP recombination target site becomes integrated into the genome. Note that the present claims call for the first FLP target recombination site to be precisely placed else the precise location of the integrating DNA is not definable. In this regard applicant's comments are not persuasive since the claims require the integrating event to be precise and anything other than integration at a predetermined sequence on a predetermined chromosome is a random event. Random events are not precise nor specific.

The rejection of claims 25, 26, 28, 42-46, and 48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The comments in the brief (item 3, pages 8-9) have been considered but are not persuasive. First the claims (e.g., claim 25) require "precise" targeting and even as argued in the brief, it does not show nor demonstrate how the first nucleic acid FLP recombination target site is precisely targeted since as presently recited, the claim also calls for precise targeting of the first DNA as the "a nucleic acid" refers to both the first and second DNA fragments whereas appellant argues that does not, however, appellant's amendment's to the claims do not reflect appellant's statements in the brief. Insofar as the first paragraph at page 9 refers to an amendment, that amendment is the amendment filed on 20 July 1995 (see brief at page 3, last two paragraphs) which is not entered as previously communicated to appellant. Discussion of the unentered amendment is not persuasive nor applicable to claims on appeal not containing that amendement. The comments in the response are not persuasive.

The rejection of claims 25 and 28 under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Golic *et al.*

The comments in the brief (item (4) at page 9) have been considered as to claims 25 and 28, but are not persuasive as to the "excision" argument as the reference indicates that the FLP and FRT were integrated into the genome (page 499) and integration is not excision and is anticipatory since the Golic *et al.* reference taken in entirety indicates that the authors expected it to work in other organisms

and that other organisms included mammalian systems as Golic *et al.* indicated (page 499 right column) that a protein evolved to function in a eukaryotic cell (i.e., the yeast FLP, FRT, and recombinase wherein yeast is a eukaryotic cell) would be expected to work in a eukaryotic cell such as that of a fruit fly as well as in a mammalian system as a mammalian system is composed of eukaryotic cells. It is also noted that Golic *et al.* indicate *cre* and *lox*, however, these do not teach away from the present invention, rather they indicate analogous systems and analogous systems that function to perform site specific recombination is not a teaching away from the invention as analogous systems that work in the same manner as the yeast FRT/FLP recombinase lend support to the Golic *et al.* disclosure as supporting the fact that the authors expect it to work. Thus, the comments as to item 4 are not persuasive.

The comments regarding obviousness and the Golic *et al.* reference in item 5 (pages 9-12) have been considered. The comment (paragraph briding pages 9-10) that Golic *et al.* do not disclose or suggest mammalian cells with FLP/FRT is noted but is not persuasive because the reference indicates that the authors expected it to work in other organisms. The other organisms included mammalian systems such as discussed at page 499 (right column) that a protein evolved to function in a eukaryotic cell (i.e., the yeast FLP, FRT, and recombinase wherein yeast is a eukaryotic cell) would be expected to work in a eukaryotic cell such as that of a fruit fly as well as in a mammalian system as a mammalian system is composed of eukaryotic cells which is a more complex system that of yeast or of fruit flies where there is explicit discussion of mammalian cells. As to the argument of different systems, it is not persuasive because the yeast system as put forward in the Golic *et al.* reference is closer to mammalian systems since the yeast FRT/FLP is for a eukaryotic cell and a mammalian cell is a eukaryotic cell. The reference also indicates that the bacterial *cre/lox* functioned in mammalian cells where from the Golic *et al.* reference, it would have been anticipated (anticipation being the epitome of obviousness) if not obvious to have expected that the FRT/FLP yeast system which is more closely related to mammalian systems to work in a mammalian system as is evident from the disclosure of the Golic *et al.* reference.

At page 10 first full paragraph, the brief argues nonobviousness as to the Golic *et al.* reference. When the reference is considered for all that it teaches and suggests, the assertion of rare

and difficult made in the brief as to the Golic *et al.* reference regarding recombination (for which appellant has not set forth where in the reference that statement of rare and difficult is found or supported) is not persuasive as the cells perform that feat every time they divide and the Golic *et al.* reference demonstrates that the process of using the yeast FLP/FRT works and indicate that they expect it to work. The remarks also assert that there is a relative complexity factor between the *Drosophila* genome compared to the human genome. So noted, however, both genomes still only use A, T, G, and C and, thus, the genomes are of equivalent complexity as each uses the same four (4) bases. In the last paragraph of page 10, it is noted that the brief expands upon the "complexity" argument, however, appellant's comment does not by arguing complexity demonstrate how DNA complementary to DNA encoding FRT/FLP would not hybridize to DNAs encoding FRT/FLP. In the last paragraph of page 10, the brief also asserts that the human genome statistically is more likely to have FLP recombinase sites (i.e., there is an increased possibility that DNA encoding the FLP recombination target site would recombine since there are more sites for that recombination naturally occurring the geneome). Thus, the brief presents its own contradictory statements The issue here is that these sites would recombine. Thus, it is not as appellant argues, surprising that recombination occurs. As to the argument of severely limiting the ability of the invention to work, that comment is also not persuasive as the second DNA is targeted to FLP recombination target sites. Thus, where ever they are in the genome, that is where the prior art suggests that they would be targeted. This is especially so since the present application does not demonstrate nor provide guidance as to how the FLP recombination target sites would not have multiply and randomly integrated into the genome nor how the initial integrating event for one and only one FLP recombination target site is targeted to a presented DNA sequence on a preselected chromosome and to nowhere else. Note that even in the present application example 2, the site of integration is unspecified and not determined prior to that integrating event - i.e., there is no specificity for the initial integration event and where the initial event set forth in the present application has no specificity, it is not precisely targeted (see the admission in the first sentence of the paragraph bridging pages 6-7) whereas the cited reference discloses that the recombinase acts site specifically to a preexisting site. As to the final sentence in the last paragraph of page 10, the same system (i.e., the FLP and FRT from yeast) is used in the cited reference and in the present appliation, the physical, chemical, biological and informational properties of the same FRT and FLP DNA is the same, not different. Thus, the comments at page 10 are not persuasive.

In the first paragraph of page 11, the brief argues that there is no requirement for two different DNAs to interact. This is not persuasive and is erroneous in view of appellant's claims. For example, in claim 25, the first nucleic acid (i.e., a DNA) contains the FLP recombination target site and is introduced into the genome of the cell for the site to become inserted into the genome, that DNA interacts with the genomic DNA and is thus, an interaction of two (2) different DNA polymers. Here, the Golic *et al.* reference indicates mating the flies which is a step of introducing into the cells which are the male or female gametes the DNA encoding the FLP and/or the FRT from its counterpart gamete. Thus, the comments are not persuasive.

The second full paragraph at page 11 of appellant's brief argues that there is no disclosure or suggestion in the Golic *et al.* reference as to mammalian cells. This is not persuasive because the Golic *et al.* reference indicates that "we expect that it will work in other organisms as well" to expect the process to function in other organisms which are higher eukaryotes (page 499, left column) where mammalian cells (page 499 right column) are known higher eukaryotic cells. Here, as to other organisms, the yeast system as put forward in the Golic *et al.* reference is closer to mammalian systems since the yeast FRT/FLP is for a eukaryotic cell and a mammalian cell is a eukaryotic cell. The reference also indicates that the bacterial *cre/lox* functioned in mammalian cells where from the Golic *et al.* reference, it would have been anticipated (anticipation being the epitome of obviousness) if not obvious to have expected that the FRT/FLP yeast system which is more closely related to mammalian systems to work in a mammalian system as is evident from the disclosure of the Golic *et al.* reference. The comments in the last paragraph of page 11 of the brief are not persuasive.

The rejection of claims 25, 26, 28, 42-46, and 48 under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.*

The arguments in appellant's brief (pages 12-13) have been considered but are not convincing. In the first and second full paragraphs of page 12, the brief asserts that Sauer describe a very different system, that of *cre* and *lox* for bacteria and that there is no guidance to a different recombination system which is not persuasive because the Sauer reference demonstrates that the bacterial system functions in eukaryotic cells (mammalian cells are eukaryotic cells and yeast cells are

also eukaryotic cells). Here, the recombination systems cited in the combined references have been demonstrated to function in eukaryotic cells are expected to function in eukaryotic cells where Golic *et al.* the reference indicates (page 499) mammalian systems (such as *cre/lox* were demonstrated to effect recombination in mammalian cells) were known. It is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation which would have resulted in a process for producing the host organism as well as integration into the genome (wherein Golic *et al.* indicate at page 499 that that a protein (obviously encoded by a DNA) that has evolved to function in a eukaryotic cell might be expected to catalyze recombination more efficiently between target sites integrated in eukaryotic chromosomes as for example the disclosed FLP recombination systems. Here, the Golic *et al.* reference explicate provides motivation and expectation of success in other systems such as mammalian systems (page 507) by the indication that "We expect that it will work in other organisms as well, enhancing the methods of genetic analysis in otherwise more difficult systems" where mammalian systems (Golic *et al.* at page 499) certainly refer to mammalian systems. Thus, the systems are not divergent as asserted in the response as the function and functional domains of the DNA in the *cre/lox* and FRT/FLP have the same/analogous features, characteristics, and properties.

It is noted that the paragraph bridging pages 12-13 of the present brief assert that reliance upon the Golic *et al.* reference is improper since it deals with different systems, however, this is not persuasive because the yeast system as put forward in the Golic *et al.* reference is closer to mammalian systems since the yeast FRT/FLP is for a eukaryotic cell and a mammalian cell is a eukaryotic cell. What is of import is that the Sauer patent demonstrates that the bacterial *cre/lox* functioned in mammalian cells, from the Golic *et al.* reference, one of ordinary skill in the art would have expected the more FRT/FLP yeast system which is more closely related to mammalian systems to work in a mammalian system as is plainly evident from the disclosure of the Golic *et al.* reference. Thus, the comments in the present appeal brief are not persuasive.

The rejection of claims 25, 26 and 28 under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.* as applied to claims 25, 26, 28, 42-46, and 48 above, and further in view of Palmiter *et al.*

The present brief on appeal contains no arguments traversing the above indicated ground of rejection. It is noted that the present appeal brief in "VIII. GROUPING OF THE CLAIMS" indicates that these claims were to be considered separately, however, this is the section for which there needs to be a discussion from appellant as to the separate patentability but for which there is no discussion at all in the brief in the section "IX. ARGUMENT". Thus, there is no reason to treat these claims as separately patentable from claims 25, 26, 28, 42-46, and 48 as a group. All of the claims should be treated as a single invention and fall in view of the indicated rejections.

For the above indicated reasons, the above rejections should be affirmed.

Respectfully,

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GROUP 1800

Christopher Low
8 December 1995